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ASSESSING THE EFFECTS OF PHYSICAL ACTIVITY ON CHILDREN AND ADOLESCENTS HODGKIN'S LYMPHOMA SURVIVORS: A SYSTEMATIC REVIEW

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Abstract:
Physical activity can improve metabolism, lung functionality, aerobic capacity, physical fitness components and quality of life among children and adults diagnosed with cancer. The daily practice of physical activity and physical fitness levels are important factors to cancer care and prevention, showing positive effects on the immune system and hematologic malignancies. Hodgkin's lymphoma is a cancer of the lymphatic system, originated from B lymphocytes (a type of white blood cell) present in the lymph nodes, spleen, bone marrow, blood and numerous other organs. This system has a defense function, protecting organism from external agents and diseases. The aim of this systematic review is to analyze the effects of physical activity on fatigue, physical fitness levels and quality of life in children and adolescents Hodgkin's lymphoma survivors. The PRISMA protocol was used to conduct a systematic review of SportDiscuss, PubMed, Scopus, Web of Science and Pedro databases. 4 articles met inclusion criteria (randomized controlled trials, pre-post intervention studies with and without control group, pilot studies or preliminary studies; full-text and peer-reviewed studies; diagnosis of lymphoma during childhood or adolescence; studies using validated assessment tools or a combination of validated and non-validated tools; studies including physical activity, physical fitness and quality of life as outcomes; studies focusing Hodgkin Lymphoma exclusively; studies published in English). Results evidence a progressive decline in physical activity levels, a progressive decrease in VO_2max, increased fatigue, muscular strength reduction, and major risk of cardiovascular diseases in Hodgkin's Lymphoma survivors. Future research should clarify the effects of physical activity on HL management and etiology, to reach definitive conclusions and develop specific policy recommendations.

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1. Introduction

The decline in levels of physical activity in children and adolescents is a health-global priority (Abarca-Gómez et al., 2017), having a significant effect on chronic-degenerative disease development in middle-adult age (Zhang et al., 2019; Yu et al., 2018; Bhaskaran et al., 2018). The health-related benefits of physical activity and physical fitness levels include BMI management, (Al-Khudairy et al., 2017), cardiovascular system improvement (Abrignani et al., 2019) muscle and skeletal strengthening (Alves et al., 2019), but also mental health and well-being (Hosker et al., 2019), reducing depression and anxiety (Pascoe et al., 2019) and improving cognitive and academic performances (Singh et al., 2019).

Recent findings suggest a changing in patterns of cancer development, identifying associations between diet and physical activity with one or more cancers (Wiseman, 2018; World Cancer Research Found, 2018). Physical activity can improve health, metabolism, aerobic capacity, and quality of life among children and adults diagnosed with cancer (Brunet et al., 2018; Van Dijk-Lokkart et al., 2019; Kowaluk et al., 2019).

The daily practice of physical activity and physical fitness levels are important factors to cancer care and prevention, showing positive effects on the immune system and hematologic malignancies (Sitlinger et al., 2020; Matthews et al., 2020; Munsie et al., 2019).

According to the National Cancer Institute lymphoma is a term used to identify cancer involving B-cells of the lymphatic system (NIC), differing in two main types: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).

Hodgkin's lymphoma (HL) is defined by the National Cancer Institute (NIC) as one of "*the few pediatric malignancies that shares aspects of its biology and natural history with an adult cancer*", and it is one of the most curable cancer in childhood and adult age (approximately 90% to 95%). Hodgkin lymphoma involves 6% of total childhood cancers (NCI). The incidence of HL is age-related, with a higher prevalence in children and young aged 14 years, and immune system maturation and development dependent, increasing in individuals with immunodeficiency (Crombie et al., 2019).

A recent review shows the following results (a) exercise can invigorate B cells; (b) acute exercise can mobilize immature B-cells to the greatest extent; (c) an increase the number of total B-cells after exercise; (d) invigorate B-cells after exercise; (e) exercise benefits on vaccines response, related to improved B-cells functions; (f) an increase frequencies of B-regulatory cells mediating the immune responses (Sitlinger et al., 2020). In particular, aerobic exercise and cardiorespiratory physical fitness training can be efficacy to promote changes in the immune system, influencing the response of leukocytes, lymphocytes, lymphocyte subpopulations, interleukins, NK cells and immunoglobulins (Gonçalves et al., 2020). Findings reveals that B-cells activation is an

important factor contributing to B-cell Lymphoma development, mediating the role of the immune system for BMI and physical activity (Saberi Hosnijeh et al., 2020).

The aim of this systematic review is to analyze the effects of physical activity on fatigue, physical fitness levels and quality of life in children and adolescents Hodgkin's lymphoma survivors.

2. Methods

Using the PRISMA model, "Preferred Reporting Items for Systematic reviews and Meta-Analyzes" (Moher, Liberati, Tetzlaff, & Altman, 2009) a systematic literature review was performed to analyze the relationship between physical activity and physical fitness related quality of life in children and adolescents Hodgkin's lymphoma survivors.

The literature search was performed by consulting six electronic databases (SPORTDiscuss, PubMed, Scopus, Web of Science, Google Scholar and Pedro), associating the terms "Physical Activity" AND "Hodgkin Lymphoma".

The last bibliographic search dates back to 12/10/2020. The articles identified from the literature search were selected only if they were related to Hodgkin's lymphoma.

To make the bibliographic search more complete and not to exclude some works, the following gray literature was consulted:

- Exercise sciences;
- Sports Science: International Scientific Journal of Kinesiology;
- Research desk;
- Kinesiology: International Journal of Fundamental and Applied Kinesiology;
- Journal of physical education and sport
- Montenegrin journal of sports science and medicine;
- Analele Universităţii din Oradea. Facicula Educaţie Fizică şi Sport.

Only articles already published, peer-reviewed and in full-text were considered. After removing the duplicates, the lead author selected the relevant articles based on the title and abstract analysis. The authors jointly contributed to resolving uncertainties about the relevance or otherwise of some studies. Subsequently, the full-text texts were analyzed to identify those capable of satisfying the inclusion criteria. All studies that met the inclusion criteria were then analyzed separately and independently by the author 1 and 2. Any disagreements on the selection of works were resolved through a critical discussion between the authors. The synthesis and analysis of the data of the studies included in the systematic review was carried out by the author 2. Data relating to (I) author / year of publication; (II) age diagnosed lymphoma; (III) age at assessment; (IV) received medical treatment and disease stage; (V) smoking habit; (VI) levels of physical activity; aim and scope; (iii) sample, (iii) study design; (iv) assessment tools; (v) significant results were reported.

2.1 Inclusion Criteria

Articles meeting the following inclusion criteria were included in the systematic review: (a) randomized controlled trials (RCTs), pre-post intervention studies with and without control group, pilot studies or preliminary studies; (b) full-text and peer-reviewed studies; (c) diagnosis of lymphoma during childhood or adolescence; (d) studies using validated assessment tools or a combination of validated and non-validated tools; (e) studies including physical activity, physical fitness and quality of life as outcomes; (f) studies focusing Hodgkin Lymphoma exclusively; (g) studies published in English. Literature reviews, lectures, mastery thesis, monographs, conference papers, dissertations and similar documents were excluded.

2.2 Risk of Bias

The following criteria were used to assess the quality and risk of error of the studies considered: (a) explanation of the sample recruitment process; (b) validity of the assessment tools; (c) drop-out of less than 30% of the total pre / post intervention sample; (d) analysis of variance and co-variance; (e) description of the results obtained and reported effect-size; (f) precision of the effects obtained (eg. confidence interval). Each item was assigned a score of 2 if the study provided clear and precise information; 0 if the requested information was not reported; 1 the information was not entirely accurate.

The works were then tagged as "high" or "low" quality studies. The present review only considered studies identified as "high quality" which satisfy at least 3 out of 6 items (equal to or greater than 50%).

3. Results

The initial database research produced 518 results; 5 additional works have been added deriving from other sources. After removing the duplicates (85), 438 articles were analyzed based on title and abstract, and 30 articles were analyzed in full text for eligibility (Figure 1).

26 studies didn't meet the inclusion criteria: 7 didn't provide physical activity assessment or intervention (27%), 8 age of the sample or not specified age at diagnosis (31%), 6 non-specific focus on Hodgkin's lymphoma (23%), 5 conference paper, thesis and abstract (19%).

Four studies were selected, analyzed and included in the review process, evaluating physical activity and physical fitness levels in HLS (Hodgkin's Lymphoma survivors). Two studies are cross-sectional, describing fitness and quality of life in HLS focusing on cardiovascular status and risk of cardiovascular diseases, with and without GC (Wogksch et al., 2019; Adams et al., 2004), and the others two studies are longitudinal, involving the evolution of physical fitness parameters, fatigue and cardiovascular disease over time (Macpherson et al., 2015; Jones et al., 2014).

All studies were conducted after medical treatment of lymphoma (chemotherapy and radiation therapy). Age at diagnosis range from 13.8 (Wogksch et al., 2019) to 28.7

(Jones et al., 2004), while age at assessment range from 10 (Wogksch et al., 2019) to 27.5 years after diagnosis (Adams et al., 2004); only the study of Macpherson et al. (2014) was conducted immediately after medical treatment. Sample mainly consists of stage II disease in two studies (Macpherson et al., 2015; Adams et al., 2004); Jones et al. (2014) considers the severity of CV events for sample recruitment, and Wogksch et al. (2015) doesn't specify the stage of disease.

The proportion of current, past and non-smoker are similar in all of 3 studies reporting related data (Wogksch et al., 2019; Jones et al., 2014; Adams et al., 2004), with a large percentage of non-smoker or past smoker (about 80%). Physical activity surveillance reveals that most of HLS are insufficiently physically active, not respecting international recommendations and guidelines (Wogksch et al., 2019; Macpherson et al., 2015; Jones et al., 2014).

Assessment involves a mixed assessment, integrating and combining motor test (Sit and reach test, 6-min walk test, exercise stress test), objective methods (ECG, echocardiogram, ECG Holter monitor, muscular strength etc.) with subjective methods (self- report) for the evaluation of physical activity levels and quality of life.

Studies reveal a progressive decline in endurance, a decrease in VO_2max, increased fatigue, and muscular strength reduction in HLS; risk cardiovascular disease are inversely related to levels of physical activity, with the 51% of reduction for PA $\geq$ 9 MET hours/week $^{-1}$. According to smoking habit no significant results were found. Table 1 shows a more detailed analysis of the studies reviewed.

Table 1: Physical Activity, Fitness Levels and Quality of Life in Childhood and Adolescents HL Survivors

Authors, Years	Sample	Age at Diagnosis	Age at Assessment	Medical Therapy and Disease Stage	Smoking Habit	Levels of PA	Aim and Scope	Study Design	Assessment Tools	Results
Wogksch et al., 2019	ES= 336 HLS; CG= 327 NHL; Median age= 36.7, range 19.1 to 60.6 years old	Mean age: 13.8 years	At least 10 years from original diagnosis	Chemotherapy and radiation therapy; Stage disease no specified	EG= 22.0% (current), 19.0% (past) and 59.0% (never)	EG= 53.6% (physically active) CG= N/A	Describing fitness and associated health-related quality of life in survivors of childhood Hodgkin lymphoma (HL) compared with a control population without childhood cancer	Cross Sectional Study	Anthropometrics, muscular strength (Biodex Medical Systems, Shirley, NY), muscular endurance (knee work fatigue), flexibility (Sit and reach test), and cardiopulmonary endurance (6-min walk test), Peripheral nervous system integrity (Total Neuropathy Score; Wampler et al., 2006) and balance (Ford-Smith et al., 1995), and quality of life (Medical Outcomes Survey 36-Item Short Form; Reulen et al., 2006)	↓ endurance and neuropathy in male survivors ($P < 0.01$); ↓endurance ($P < 0.01$), quadriceps strength ($P < 0.01$), and neuropathy ($P < 0.01$) in female survivors; - Quadriceps strength ($P < 0.01$), endurance ($P < 0.01$), and neuropathy ($P < 0.01$) associated with lower physical component on the Health Related Quality of Life.
Macpherson et al., 2015	M= 44, F= 59, mean age= 15.46yrs (range 13-21 years)	15.46 years, range 13 to 21 years old	12- and 36-months post-therapy	Chemotherapy and radiation therapy; Stage II disease (65%)	N/A	End of therapy= 2.74±2.17 DWE; 12 months post-therapy= 2.70±1.99 36 months post therapy= 2.92±2.16	Exploring the trajectories of and relationship between amount of exercise and fatigue	Longitudinal Study	Child Cancer Survivors Surveillance questionnaire (Robison et al., 2005)	↑ Exercise and fatigue over time; ↑amount of exercise at end of therapy, at 12 ($p = 0.02$) and 36 ($p = 0.0008$) months post-therapy

Jones et al., 2014	N= 1187, survivors of HL; median age: 31.2 years; range, 18.0 to 48.9 years at study entry	16.7 years, range 8.2 to 28.7 years old	41.9 years, range 21.9 to 57.9	Chemotherapy and radiation therapy;	15.1% (current), 27.4% (past) and 57.5% (never)	35.9% = 0 MET x hours/week^{-1} 26.7% = 3 to 6 MET x hours/week^{-1} 22.7% = 9 to 12 MET x hours/week^{-1} 14.7% = 15 to 21 MET x hours/week^{-1}	Investigating the association between exercise and risk of cardiovascular events in adult survivors of HL participating in the Childhood Cancer Survivor Study	Longitudinal Study	Youth Risk Behavior Surveillance Survey, single item (Troped et al., 2007)	↓ incidence of any CV event across increasing MET categories (*Ptrend* = .002); ↑ physical activity (i.e., ≥ 9 MET hours/week $^{-1}$) was associated with the 51% reduction in the risk of any CV event in comparison with not meeting the guidelines (p =.002)
Adams et al., 2004	N= 48, M= 23, F= 25;	16.5 years, range 6.3 to 25.0 years old	14.3 years, Range to 5.0 to 27.5	Stage II disease (64.6%)	27.0% (current), 14.5% (in the last 4 weeks) and 58.5% (never)	N/A	Assessing cardiovascular status Hodgkin's Lymphoma survivors and the increased risk for cardiovascular diseases	Cross Sectional Study	Echocardiogram, ECG, exercise stress test, 24-hour ECG (Holter monitor), Short-Form 36 quality-of-life instrument (Ware & Sherbourne, 1992)	↓ VO2max during exercise (<20 mL/kg/m2) in 30% of survivors; VO2max correlated with increasing fatigue, increasing shortness of breath (both, r = - 0.35; P = .02), and decreasing physical component score on the SF-36 (r = 0.554; P = .00017).

Note: HLS= Hodgkin's Lymphoma Survivors; NHLS= No Hodgkin's Lymphoma; DWE= days of exercise for week; MET= metabolic equivalent on task; PA= physical activity; ↓= decrease; ↑= increase

4. Discussion

The aim of the current research was to present an updated review of the literature on levels of physical activity, physical fitness and quality of life in young Hodgkin's Lymphoma survivors. Results highlights that an increase in fatigue, a decrease in VO_2max, muscles strength and endurance levels, and lower physical component associated with quality of life.

A recent review underlines that (a) higher level of physical activity seems to be inversely associated with lymphoma development (compared to the lower PA level); (b) female subjects appear to better benefit from higher PA levels than boys (Davies et al., 2020). At the same time, a large percentage of adolescents and young adult cancer survivors (AYACs) do not meet the lifestyle guidelines and recommendations for PA, BMI, and/or smoking, involving several late effects and/or comorbidities (Bøhn et al., 2020).

Moreover, young Hodgkin's Lymphoma survivors' evidence high levels of persistent physical fatigue, emotional distress, and cognitive decline, with a progressive reduction in the quality of life (Mounier et al., 2019; Trachtenberg et al., 2019). Despite the well-known relationship between aerobic capacity and lung function, the improvements in lung function are correlated with highest physical fitness levels during childhood and adolescence through early adulthood, and being active during evolutive age is associated with improved lung function in adulthood (Puente-Maestu & Stringer, 2018).

The study of Deisenroth et al. (2016) underlines a significant decrease in strength levels (especially in lower extremities) and quality of life in children with cancer, already during the primary medical treatments. The study of Garcia-Hermoso et al. (2020) reveals that cardiorespiratory fitness is inversely correlated with total white blood cells (WBC), such as neutrophils, lymphocytes, monocytes, basophils, and eosinophils, and MVPA in boys. Furthermore, highest levels of cardiorespiratory fitness are associated with a normal range of WBC, strengthening the immune system of children and adolescents (Garcia-Hermoso et al., 2020).

The study of Hooke et al. (2019) evaluates the effects of PA and fatigue in children and adolescents with cancer (acute lymphoblastic leukemia, lymphoma, and solid tumors). Results show s progressive decline in trends of fatigue during treatments of ALL (acute lymphoblastic leukemia) and lymphoma, and an increase in children with solid tumors, even if PA levels were unchanged in all sample. Recent findings suggest that childhood BMI is positively correlated with hematologic malignancies, and highest childhood BMI is a determinant of Non-Hodgkin lymphoma and diffuse large B-cell lymphoma (Celind et al., 2020).

Kowaluk et al. (2019) assesses PA and quality of life in a sample of children undergoing cancer treatment, during and after treatment completion, finding the following results: (a) during treatment children didn't following MVPA physical activity guidelines and recommendations (at least 60min per day at week); (b) after treatment

children spent at least 30 minutes per week in MVPA, while healthy children were physically active at least 5 days per week; (c) quality of life of children with cancer is significantly lower and different from the quality of life of healthy children.

A research investigating pattern of physical activity in childhood with cancer shows that PA barriers persist both during and after therapy, with children preferring short-term activity (10-20 minutes), low-intensity activity (i.e. walking), and carried out in the afternoon (Ross et al., 2018).

4. Conclusion

The present review underlines a progressive decline in endurance and muscular strength, increasing fatigue and negatively influencing quality of life in childhood and adolescents HL survivors. The data are quite worrying and sedentary lifestyles, associated with a reduction in the quality of life, could have negative consequences on the general state of health, impacting even more the health system in the medium-long term. Daily practice of physical activity, as well as active lifestyles, could have an important role and positive effects both on prevention of HL during childhood and adolescence, and enhance physical fitness status after medical treatment (chemotherapy and radiotherapy). Movement specialist, expert in motor sciences and health-care professionals should encourage adults to be physically active and promote active lifestyles to maintain and obtain better health status. Low-intensity aerobic activity (i.e. group of walking) and low-impact muscle strengthening activity involving total body movement (i.e. yoga, tai-chi etc.) could be useful to promote physical fitness components, especially during the first period after cancer treatment. Special attention should be given to youngest, as the BMI management, the acquisition of active lifestyles, the development of motor components and a positive attitude towards physical activity, with all positive consequences on immune system, can be best promoted. Our study illustrates the necessity of guidelines, social, institutional and parents support for improving health-related behavior in cancer survivors, in order to improve their life beyond cancer. Further future research should clarify the effects of physical activity on HL management and etiology, to reach definitive conclusions and develop specific policy recommendations.

Conflict of Interest Statement
The authors declare no conflicts of interests.

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